Reviewer's report

Title: Dose patterns in subjects chronically exposed to opioids: a large cohort study in the United States

Version: 2 Date: 20 October 2009

Reviewer: Gary Franklin

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This is a population-based study of opioid use using large insurance databases. There are a number of critical issues that should be addressed.

Major compulsory revisions:

1. The "participants" presumably only include those who have continuous coverage by a commercial insurer through employment; as such, anyone who leaves employment related to pain-related disability would likely not be included here. For example, besides the Medicaid population, this data source would exclude thousands of injured workers treated for chronic pain through workers' compensation insurance. The study source used here would also exclude the large number of employed uninsured persons. As the authors intimate, the rather rapid fall off of numbers among the continuously followed cohort may represent the worst patients leaving the system for another method of coverage. Thus, this study may severely underestimate counts of those most likely to have disabling pain, and thus those most likely to actually develop problems with long term opioid use. These issues should be spelled out in much greater detail as limitations. In fact, the title would really most properly be, "Dose patterns in employed subjects..."

2. The authors have defined the index case as at least 2 prescriptions of opioids within 6 months. But what one would really be interested in is the subpopulation which started out as an incident pain case, but then developed chronic pain. Chronic pain would be pain beyond 3 months. This is the principal population for which dose escalation is of substantial concern. Unfortunately, in the absence of indication information, this study cannot really clearly identify this important subpopulation. The methods used by Von Korff in the cited paper, as well as by Boudreau et al (Pharmacoepi Drug Safety 2009), should be repeated here to try to reproduce findings across studies.

3. There is no mention whatever in this manuscript of the studies related to substantial morbidity and mortality from unintentional poisoning by opioids; it is these findings that have led to the FDA REMS response, and to public health concern. The authors cannot conclude from the data analyzed here, and with the substantial limitations enumerated above, that "success of the adequate patient selection and careful evaluation by health care providers" can be construed from these findings. In fact, there is no evidence whatever that, beyond an initial history
and physical, that any of the reasonable standards are being followed routinely. These would include routine urine drug monitoring, screening for past/current substance abuse, use of a treatment agreement, and tracking pain and function.

4. There is mention of efficacy of opioids short term in the Introduction, but no mention of the paucity of data on lack of efficacy long term.

5. The emphasis on median dose throughout is not really appropriate. It is likely that a smaller tail with inappropriate escalation is what is going on, but that is likely being missed here.

6. What is the average dose over time of only the Schedule II longer acting opioids? These are likely the patients at the greatest risk for more dangerous escalation.

7. What % of patients achieve doses of over 100 mg/day in each 6 month period? There is a paper in press that will demonstrate a 10 fold increase in risk of morbidity and mortality at that morphine equivalent dose.

8. Who considers 50 mg to be a low dose? This is the average dose reported in several population-based studies. I would delete that statement.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare I have no competing interests